DOD PHARMACY AND THERAPEUTICS COMMITTEE RECOMMENDATIONS

INFORMATION FOR THE UNIFORM FORMULARY BENEFICIARY ADVISORY PANEL

I. UNIFORM FORMULARY REVIEW PROCESS

Under 10 United States Code § 1074g, as implemented by 32 Code of Federal Regulations 199.21, the DoD Pharmacy and Therapeutics (P&T) Committee is responsible for developing the Uniform Formulary (UF). Recommendations to the Director, TMA, on formulary status, pre-authorizations, and the effective date for a drug's change from formulary to nonformulary (NF) status receive comments from the Beneficiary Advisory Panel (BAP), which must be reviewed by the Director before making a final decision.

II. UF CLASS REVIEWS—TOPICAL PAIN AGENTS

P&T Comments

A. Topical Pain Agents—Relative Clinical Effectiveness and Conclusion

The P&T Committee evaluated the Topical Pain agents subclass, which is comprised of lidocaine 5% patch (Lidoderm), diclofenac 1% gel (Voltaren), diclofenac 1.5% solution (Pennsaid), and diclofenac 1.3% patch (Flector).

The Topical Pain agents are a subclass of the Pain Agents UF drug class, which includes the Narcotic Analgesics and oral Non-Steroidal Anti-Inflammatory drugs (NSAIDs).

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) the following:

- Lidoderm is effective as first line and/or combination therapy for the management of its orphan indication—postherpetic neuralgia (PHN). There is insufficient evidence supporting use of Lidoderm for other neuropathies (e.g., diabetic neuropathy, HIV-associated neuropathy, complex regional pain syndrome); however, several professional guidelines support its use. There is a paucity of data regarding use of Lidoderm for other off-label conditions, including widespread or deep pain conditions such as fibromyalgia or chronic pain associated with osteoarthritis.
- A review of Military Health System (MHS) prescribing trends showed a high discontinuation rate for Lidoderm, with a similar prevalence between unique user new starts and discontinuations. A Pharmacy Outcomes Research Team (PORT) analysis showed that Lidoderm is commonly

prescribed in the MHS for off-label, non-supportable uses (e.g., musculoskeletal pain) that are not associated with neuropathic pain.

- There are no head-to-head trials comparing the topical diclofenac products in terms of efficacy or safety. However, indirect evidence suggests the agents are highly interchangeable with regards to efficacy. Limited evidence suggests the agents are as effective as oral diclofenac.
- The incidence of gastrointestinal (GI) adverse events is lower with the topical diclofenac products compared to oral NSAIDs, offering a potential advantage for patients with a history of GI bleeding or peptic ulcers.
- Systemic side effects are uncommon and the most common adverse events are application site reactions, including pruritis with Lidoderm, and dry skin, erythema and pruritis with the topical diclofenac products.
- Flector is indicated for short-term use associated with acute musculoskeletal injury and is likely to be used in a younger population than Voltaren gel or Pennsaid drops.
- Pennsaid is indicated only for osteoarthritis of the knee and clinical usefulness may be limited by multiple daily dosing (four times daily).

B. Topical Pain Agents—Relative Cost-Effectiveness Analysis and Conclusion

Pharmacoeconomic analyses were performed for the Topical Pain Agent subclass, including cost-minimization analysis (CMA) and budget impact analyses (BIAs). For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted.

The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) that among topical diclofenac products, diclofenac gel (Voltaren) was the most cost-effective, based on the weighted average cost per day of treatment across all three points of service (POS), followed by diclofenac drops (Pennsaid), and diclofenac patch (Flector). Results from the CMA and BIAs showed that the scenario where Lidocaine patch (Lidoderm) and diclofenac gel (Voltaren) were designated UF, with diclofenac drops (Pennsaid) and patch (Flector) designated NF, was the most cost-effective for the MHS.

C. Topical Pain Agents—UF Recommendation

The P&T Committee recommended (16 for, 0 opposed, 1 abstained, 0 absent) lidocaine 5% patch (Lidoderm) and diclofenac 1% gel (Voltaren) remain designated with formulary status on the UF, and recommended NF status for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector), based on clinical and cost effectiveness.

D. Topical Pain Agents—Prior Authorization (PA) Criteria

After extensive discussion, the P&T Committee recommended (12 for, 4 opposed, 1 abstained, 0 absent) manual PA criteria apply to all current and new users of lidocaine 5% patch (Lidoderm). Coverage is approved for patients who have a diagnosis of postherpetic neuralgia, other peripheral neuropathic pain, and for patients with non-neuropathic pain where an occupational or clinical reason exists and other analgesics are contraindicated. Coverage is not approved for other uses of Lidoderm.

E. Topical Pain Agents—UF and PA Implementation Plan

The P&T Committee recommended (16 for, 1 opposed, 0 abstained, 0 absent) 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions.

III. UF CLASS REVIEWS—TOPICAL PAIN AGENTS

BAP Comments

A. Topical Pain Agents—UF Recommendation

The P&T Committee recommended lidocaine 5% patch (Lidoderm) and diclofenac 1% gel (Voltaren) remain designated with formulary status on the UF, and recommended NF status for diclofenac 1.5% solution (Pennsaid drops) and diclofenac 1.3% patch (Flector), based on clinical and cost effectiveness.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. Topical Pain Agents—PA Criteria

After extensive discussion, the P&T Committee recommended manual PA criteria apply to all current and new users of lidocaine 5% patch (Lidoderm). Coverage is approved for patients who have a diagnosis of postherpetic neuralgia, other peripheral neuropathic pain, and for patients with non-neuropathic pain where an occupational or clinical reason exists and other analgesics are contraindicated. Coverage is not approved for other uses of Lidoderm.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. Topical Pain Agents—UF and PA Implementation Plan

The P&T Committee recommended 1) an effective date of the first Wednesday after a 90-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions.

BAP Comment: □ Concur □ Non-concur Additional Comments and Dissention

IV. UF CLASS REVIEWS—PULMONARY II DRUGS

P&T Comments

A. Pulmonary II Drugs—Relative Clinical Effectiveness and Conclusion

The Pulmonary II Drug Class is comprised of aclidinium inhaler (Tudorza), tiotropium inhaler (Spiriva), roflumilast tablets (Daliresp), ipratropium (Atrovent HFA; Atrovent nebulized solution), and ipratropium/albuterol (Combivent, Combivent Respimat and DuoNeb nebulized solution). The two inhalation solutions, ipratropium (Atrovent) and ipratropium/albuterol (DuoNeb), are available in generic formulations.

Combivent metered dose inhaler (MDI) is one of the last available chlorofluorocarbon (CFC) MDIs on the market and will have supplies exhausted by December 2013. Its replacement is Combivent Respimat, a new CFC- and propellant-free formulation.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- Aclidinium inhaler (Tudorza) is the second long-acting muscarinic agent (LAMA) on the market. The three clinical trials used to obtain FDA approval reported statistically significant improvement in spirometric endpoints, and two of the trials reported significantly fewer chronic obstructive pulmonary disease (COPD) exacerbations with aclidinium, compared to placebo.
- For aclidinium (Tudorza), the adverse event profile appears minimal, with primarily anticholinergic events reported. However, there is limited safety data with the 400 mcg approved dose. The FDA is requiring a prospective clinical

trial to assess cardiovascular safety. Longer duration and larger comparative trials are needed to determine aclidinium's place in therapy.

- Several trials have shown the LAMA tiotropium (Spiriva) is associated with clinically significant improvements in spirometric endpoints and reductions in risk for COPD exacerbations. Tiotropium is also reported to reduce the proportion of patients hospitalized for COPD exacerbations.

- Reports of a possible link between tiotropium (Spiriva) and adverse cardiovascular (CV) events including death, stroke, and myocardial infarction have not been confirmed in prospective trials.

- Roflumilast (Daliresp) is the first oral selective inhibitor of phosphodiesterase type 4 marketed in the United States. Its FDA indication is limited to reducing the incidence of COPD exacerbations in patients with severe COPD. In two clinical trials, roflumilast was associated with statistically significant reductions in the rate of COPD exacerbations.

- For roflumilast (Daliresp), safety issues identified by the FDA included psychiatric events (including suicide), weight loss, GI upset and severe diarrhea, and nasal tumors. However, the FDA did not require additional prospective safety studies. A risk evaluation and mitigation strategy program was not required.

- Albuterol/ipratropium inhaler (Combivent Respimat) is the new propellant-free inhaler that is replacing the ozone-depleting chlorofluorocarbon (CFC)-containing Combivent metered dose inhaler (MDI). The clinical trial used to obtain FDA approval showed Combivent Respimat was non-inferior to Combivent CFC MDI in terms of improvements in spirometric endpoints.

B. Pulmonary II Drugs—Relative Cost-Effectiveness Analysis, Relative Cost-Effectiveness Conclusion, and UF Recommendation

The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF recommendations will be presented at an upcoming meeting.

V. UF CLASS REVIEWS—PULMONARY II DRUGS

BAP Comments

A. Pulmonary II Drugs—UF Recommendation

The P&T Committee reviewed proposed condition sets for contract solicitation. The cost-effectiveness analysis and UF recommendations will be presented at an upcoming meeting.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

VI. UF CLASS REVIEWS—ORAL ANTICOAGULANTS

P&T Comments

A. Oral Anticoagulants—Relative Clinical Effectiveness and Conclusion

The Oral Anticoagulant Drug Class is comprised of warfarin (Coumadin, generic), and the newer oral anticoagulants (NOACs) dabigatran (Pradaxa) and rivaroxaban (Xarelto). Another NOAC, apixaban (Eliquis) was approved in December 2012, and will be evaluated as a new drug at an upcoming meeting. Warfarin has been designated a BCF drug since before 1998, prior to implementation of the Uniform Formulary Rule in 2005.

Dabigatran, rivaroxaban, and apixaban are approved for stroke prevention in patients with non-valvular atrial fibrillation (Afib). Rivaroxaban has additional indications for prophylaxis of venous thromboembolism (VTE) in patients following hip or knee replacement surgery, and is indicated to prevent recurrent VTE in patients with deep vein thrombosis (DVT) or pulmonary embolism (PE).

A PORT analysis showed that MHS users of dabigatran have a mean age of 76 years and 91% of patients have an ICD-9 diagnosis code for Afib. MHS users of rivaroxaban have a mean age of 70 years and 41% of patients have an ICD-9 diagnosis code for Afib versus 39% of patients with a diagnosis code for hip of knee replacement surgery.

Relative Clinical Effectiveness Conclusion—The P&T Committee agreed (17 for, 0 opposed, 0 abstained, 0 absent) on the following clinical effectiveness conclusions:

- The newer oral anticoagulants (NOACs) dabigatran and rivaroxaban have advantages of predictable anticoagulant effect, fixed dosing, and fewer drug interactions compared to warfarin (Coumadin, generic). Advantages of warfarin include its long history of use, reliable reversal agent (vitamin K), and adverse effects that are predictable and manageable
- The NOACs offer a convenience to patients; laboratory monitoring for efficacy and dietary restrictions are not required. More data is needed in patients with renal and hepatic impairment. No reversal agent is available with the NOACs.
- In non-valvular atrial fibrillation (Afib), dabigatran and apixaban were superior to poorly controlled warfarin at preventing stroke and systemic embolism, including hemorrhagic stroke; rivaroxaban was non-inferior to poorly controlled warfarin for these outcomes. Intracranial bleeding was lower with dabigatran, rivaroxaban, and apixaban compared to warfarin.
- For venous thromboembolism (VTE) prevention following orthopedic surgery, rivaroxaban was superior to enoxaparin at preventing symptomatic deep venous thrombosis (DVT), but at the cost of increased bleeding.
- For prevention of VTE recurrence following DVT or pulmonary embolism (PE), rivaroxaban in two trials was non-inferior to enoxaparin/warfarin for preventing recurrent VTE, with no difference in bleeding, and was superior to placebo in one trial for extended therapy for 6–12 months.
- Due to a lack of head-to-head trials, there is insufficient evidence to determine if one NOAC has advantages over the others.
- Patients require education and clinical monitoring to ensure appropriate use and avoid adverse reactions with the NOACs. Bleeding is a concern with all the NOACs, and dabigatran is associated with dyspepsia and major GI bleeding. For warfarin, a high risk of falls is not associated with risk of subsequent major bleeding.
- It remains to be determined whether the NOACs will increase the numbers of patients currently undertreated for stroke prevention in Afib. Also unknown is whether NOACs will improve persistence rates for anticoagulation therapy.

B. Oral Anticoagulants—Relative Cost-Effectiveness Analysis and Conclusion

The P&T Committee evaluated the relative cost-effectiveness of the anticoagulant agents for stroke prevention in non-valvular Afib and for prophylaxis of VTE in patients undergoing knee or hip replacement surgery. CMAs were performed for both indications. Additionally, a cost-effectiveness analysis (CEA) evaluated the agents for stroke prevention in Afib.

- For the anticoagulant drugs prescribed, CMAs were used to compare the anticoagulant drug costs including relevant drug monitoring costs (e.g., international normalized ratio testing for warfarin and office visits).
- The CEA model was constructed based on comparisons of relevant clinical trial data from systematic reviews. The CEA model assessed the potential impact of anticoagulant treatment on the occurrence of stroke, bleeding, MI, and mortality. Results were reported as an incremental cost-effectiveness ratio (ICER) comparing the additional costs per life year gained with the NOACs dabigatran (Pradaxa) and rivaroxaban (Xarelto) in relation to warfarin.
- For the BIAs, several of the model's key assumptions were varied, with corresponding sensitivity analyses conducted. BIA results were presented to the P&T Committee. The MHS projected budgetary impact varied depending on which medication was selected for BCF, UF, or NF status.

Relative Cost-Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 against, 0 abstained, 0 absent) the following:

- Anticoagulant agents for stroke prevention in non-valvular AFib—CMA results showed that, in all scenarios, warfarin (Coumadin, generic), including drug monitoring costs, was the least costly agent. CEA results showed that the ICERs per life year gained with dabigatran and rivaroxaban in relation to warfarin were in a range that could be considered cost-effective to the MHS.
- Anticoagulant agents for DVT/PE prophylaxis in hip and knee replacement surgery—CMA results demonstrated that rivaroxaban (Xarelto) was a cost-effective alternative compared to enoxaparin (Lovenox), based on analysis of the average weighted price per day of therapy at all three POS.
- BIA results—Scenarios where all drugs remain on the UF resulted in the greatest cost-avoidance to the MHS.

C. Oral Anticoagulants—UF Recommendation

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) warfarin (Coumadin, generic), dabigatran (Pradaxa), and rivaroxaban (Xarelto) remain formulary on the UF.

D. Oral Anticoagulants GI-2—UF Implementation Period

Not applicable, as no changes in formulary tier status were recommended.

VII. UF CLASS REVIEWS—ORAL ANTICOAGULANTS

BAP Comments

A. Oral Anticoagulants—UF Recommendation

The P&T Committee recommended warfarin (Coumadin, generic), dabigatran (Pradaxa), and rivaroxaban (Xarelto) remain formulary on the UF.

B. Oral Anticoagulants GI-2—UF Implementation Period

Not applicable, as no changes in formulary tier status were recommended.

BAP Comment:	□ Concur	□ Non-concur
	Additional Comments and Dissention	

VIII. RECENTLY APPROVED U.S. FDA AGENTS

P&T Comments

A. Newer Sedative Hypnotic-1 (SED-1s) Agents: Zolpidem Sublingual Low Dose Tablets (Intermezzo)—Relative Clinical Effectiveness and Conclusion

Intermezzo is a new low-dose zolpidem sublingual (SL) formulation available in 1.75 mg and 3.5 mg tablets. Women should not receive Intermezzo doses larger than 1.75 mg. Intermezzo is specifically approved for treatment of insomnia characterized by middle-of-the-night waking followed by difficulty returning to sleep. In one study, there was a statistically significant improvement in sleep latency and total sleep time with Intermezzo versus placebo for middle-of-the-night awakening, but another placebo-controlled trial found no differences in total sleep time. No studies have been completed with an active comparator.

Relative Clinical Effectiveness Conclusion—The P&T Committee concluded (17 for, 0 opposed, 0 abstained, 0 absent) despite its unique FDA labeling for middle-of-the-night awakening compared to the other SED-1s and the potential for less next-day impairment, zolpidem SL low dose (Intermezzo) does not offer a clinically compelling advantage over the other SED-1s included on the UF.

B. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—Relative Cost-Effectiveness Analysis and Conclusion

The P&T Committee concluded (16 for, 0 opposed, 0 abstained, 1 absent) that zolpidem SL low dose (Intermezzo) is not cost-effective when compared to other

SED-1s included on the UF. The relative CMA ranking of the comparator SED-1s (ranked from most cost-effective to least cost-effective) revealed that zolpidem immediate release (IR) (Ambien IR, generics) < zaleplon (Sonata, generics) < zolpidem ER (Ambien CR, generics) < zolpidem SL (Edluar)< ramelteon (Rozerem) < zolpidem SL low dose (Intermezzo).

C. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—UF Recommendation

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) zolpidem SL low dose (Intermezzo) be designated NF due to the lack of compelling clinical advantages and cost disadvantage compared to UF products.

D. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—PA Criteria

Existing automated prior authorization (step therapy) requires a trial of generic zolpidem IR or zaleplon, the step-preferred agents, prior to the other SED-1s in new users. The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) the following PA criteria should apply to Intermezzo. Coverage would be approved if the patient met any of the following criteria:

1. Automated PA criteria: The patient has filled a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS [military treatment facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.
2. Manual PA criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

E. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—UF and PA Implementation Plan

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions.

IX. RECENTLY APPROVED U.S. FDA AGENTS

BAP Comments

A. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—UF Recommendation

The P&T Committee recommended zolpidem SL low dose (Intermezzo) be designated NF due to the lack of compelling clinical advantages and cost disadvantage compared to UF products.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

B. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—PA Criteria

Existing automated prior authorization (step therapy) requires a trial of generic zolpidem IR or zaleplon, the step-preferred agents, prior to the other SED-1s in new users. The P&T Committee recommended the following PA criteria should apply to Intermezzo. Coverage would be approved if the patient met any of the following criteria:

1. Automated PA criteria: The patient has filled a prescription for zolpidem IR or zaleplon at any MHS pharmacy POS [military treatment facilities (MTFs), retail network pharmacies, or mail order] during the previous 180 days.
2. Manual PA criteria: The patient has an inadequate response to, been unable to tolerate due to adverse effects, or has a contraindication to zolpidem IR or zaleplon.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

C. SED-1s: Zolpidem SL Low Dose Tablets (Intermezzo)—UF and PA Implementation Plan

The P&T Committee recommended an effective date of the first Wednesday after a 60-day implementation period in all POS, and 2) TMA send a letter to beneficiaries affected by the UF and PA decisions.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

X. UTILIZATION MANAGEMENT

P&T Comments

A. Tretinoin Age Limits

The P&T Committee reviewed the current age limits for tretinoin, which does not allow use in patients older than 35 years. While treatment for acne is covered by TRICARE benefits, cosmetic services and supplies are excluded from the benefit, including treatments for photoaging of the skin.

The P&T Committee recommended (16 for, 0 opposed, 0 abstained, 1 absent) removing the age limit for tretinoin products that are not exclusively labeled for cosmetic use at all 3 MHS POS (MTF, Mail Order, and the Retail Network). Acne can occur beyond age 35 years. Treatment for acne is covered by TRICARE benefits and low-cost tretinoin generic formulations are available. Tretinoin products/derivatives specifically indicated for cosmetic use as a result of the aging process (e.g., Renova, Refissa, Avage) remain excluded from the Pharmacy benefit.

XI. UTILIZATION MANAGEMENT

BAP Comments

A. Tretinoin Age Limits

The P&T Committee recommended removing the age limit for tretinoin products that are not exclusively labeled for cosmetic use at all 3 MHS POS (MTF, Mail Order, and the Retail Network). Tretinoin products/derivatives specifically indicated for cosmetic use as a result of the aging process (e.g., Renova, Refissa, Avage) remain excluded from the Pharmacy benefit.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention

XII. UTILIZATION MANAGEMENT

P&T Comments

A. Zolpidem Gender-Based Dosing

The P&T Committee discussed whether PA criteria are needed for zolpidem products, given new recommendations from the FDA in January 2013 regarding dosing in women. For women, lower dosing is recommended, as blood levels in some patients may be high enough the morning after use to impair activities that require alertness, including driving. A review of MHS zolpidem prescriptions in the last six months of 2012 showed significant use of the higher zolpidem dosages in women.

The P&T Committee recommended (17 for, 0 opposed, 0 abstained, 0 absent) to not institute gender-based dosing PA criteria for zolpidem products, and to instead educate providers of the new recommendations, and notify patients via beneficiary newsletters of the concerns regarding impaired driving and activities requiring mental alertness the morning after use. The P&T Committee recommended re-evaluating this issue in six months to review MHS prescribing trends and whether additional measures are necessary.

XIII. UTILIZATION MANAGEMENT

BAP Comments

A. Zolpidem Gender-Based Dosing

The P&T Committee recommended to not institute gender-based dosing PA criteria for zolpidem products, and to instead educate providers of the new recommendations, and notify patients via beneficiary newsletters of the concerns regarding impaired driving and activities requiring mental alertness the morning after use. The P&T Committee recommended re-evaluating this issue in six months to review MHS prescribing trends and whether additional measures are necessary.

BAP Comment: □ Concur □ Non-concur

Additional Comments and Dissention